REMARKS

Claims 37-56 were previously pending in this application. Claims 37-56 are still pending for examination with claim 37 being an independent claim. No new matter has been added.

Objection to the Disclosure

The disclosure is objected to because of several informalities. Applicants have revised the disclosure accordingly. It is noted that nucleic acid sequences having fewer than 10 nucleotides have not been assigned a Sequence ID number, according to the rules. It is believed that the rejection should be withdrawn.

Objection to Information Disclosure Statement (IDS)

The Examiner has indicated that some of the references cited on the February 26, 2004 IDS have not been considered because prior application 08/386,063 was not available to the Examiner. The Examiner requests that Applicants submit copies of the references cited in that IDS which were not initialed by the Examiner.

Applicants have met their burden for compliance with 37 CFR 1.98(a)(2). In order to advance prosecution Applicants are submitting the requested references and a new form 1449. Applicants respectfully request that the Examiner consider each of the references and return an initialed copy of the 1449 to Applicants.

Rejections Under 35 U.S.C. §112

Claims 37-56 have been rejected under 35 USC 112, for lack of enablement. According to the Examiner, it is not clear from the claim whether the claimed method requires administration of a vaccine and oligonucleotide or only an oligonucleotide, and what order the components are administered.

Claim 37 recites a method for stimulating a subjects response to a vaccine by administering an immunostimulatory oligonucleotide adjuvant as a vaccine adjuvant. The claim requires that both an oligonucleotide and a vaccine be administered. The vaccine must be administered in order for the oligonucleotide to stimulate the subjects response to that vaccine.

The specification teaches that the oligonucleotide is administered in conjunction with the vaccine. "Preferably the unmethylated CpG dinucleotide is administered slightly before or at the same time as the vaccine."

The Examiner has also asserted that no data is presented in the specification in support of the claimed use of a combination of an oligonucleotide and a vaccine, and that as a result it would require one of skill in the art undue experimentation to practice the invention. Applicants disagree.

Over 300 oligonucleotides that contained methylated, unmethylated, or no CpG dinucleotides in various sequence contexts were synthesized and examined for in vitro effects on spleen cells (representative sequences are listed in Table 1). These and many other working examples are presented in the specification. In particular the cumulative data strongly supports the use of CpG oligonucleotides as adjuvants. For instance the following data is relevant:

B cell activation as measured by ^{3}H uridine (proliferation) and IgM induction (Ab production) for instance, Table 1, Examples 1 & 2;

IL-6 & IL-12 induction (in vivo) for instance, Example 6, column 14;

Increased MHC II cell surface induction (marker of B cell activation) for instance, Column 24 & Example 1;

CpG + anti-IgM results in a 10 fold (synergistic) increase of lymphocyte activation for instance, data described in column 13; and

CpG protects B cells (WEHI-231) against growth arrest or apoptosis induced by cross-linking of the receptor for instance, column 14 & Example 7.

Thus, the specification includes numerous working examples which support the use of CpG oligonucleotides as adjuvants.

The office action also asserts that the term vaccine is broad, encompassing viral, bacterial, fungal, protozoal and cancer antigens. Applicants agree that the term is broad, but assert that it is a reasonable scope based on the findings of the invention. As described above, Applicants are the first to discover that CpG oligonucleotides promote an antigen specific immune response, and are thus useful as vaccine adjuvants. The data presented in the

specification supports this finding. Applicants are entitled to claim the full scope of the invention.

The Examiner has cited Threadgill et al for the proposition that CpG oligonucleotides do not function as adequate vaccine adjuvants for bacterial polysaccharide vaccines. Applicants disagree.

Threadgill et al used a CpG dose of 250-500ug/mouse, which is a gross excess, and well into the toxic range. The usual adjuvant dose for a mouse is in the range of 1-50ug/mouse, and 500ug is a dose that is highly effective for vaccinating a human (eg., see Cooper, CL, Davis, HL, Morris, ML, Efler, SM, Al Adhami, M, Krieg, AM, Cameron, DW, and Heathcote, J: CpG 7909, an Immunostimulatory TLR9 Agonist Oligodeoxynucleotide, as Adjuvant to Engerix-B® HBV Vaccine in Healthy Adults: A Double-Blind Phase I/II Study. *Journal of Clinical Immunology.* 24(6):693-702, 2004). Furthermore, it has been shown that CpG promotes shifting of the Ab response from the immature IgM isotype to the more mature IgG isotype. As a result, the IgG isotype is usually measured. Threadgill et al surprisingly, did not measure the IgG response to the antigen, they only measured IgM. IgG is generally considered most desirable for a vaccine.

Additionally, although Threadgill et al report that CpG ODN are not useful adjuvants for polysaccharides, their key conclusions have since been refuted by other investigators. Recent reports using "normal" doses for vaccinating mice and assaying for IgG show adjuvant effects, even with a variety of polysaccharide antigens, especially when they are formulated or conjugated. For instance, the following references address some of these issues.

Chu R S et al; CpG oligodeoxynucleotides act as adjuvants for pneumococcal polysaccharide-protein conjugate vaccines and enhance antipolysaccharide immunoglobulin G2a (IgG2a) and IgG3 antibodies; Infection and immunity (2000 Mar), 68(3), 1450-6 describes pneumococcal polysaccharide-protein conjugate vaccines that elicit antipolysaccharide antibodies. Chu et al demonstrate significant adjuvant activity of CpG ODN for antibody responses against Streptococcus pneumoniae polysaccharide types 19F and 6B induced by conjugates of 19F and 6B with the protein carrier CRM(197). Adjuvant effects were not observed with control non-CpG ODN. Thus, CpG ODN significantly enhanced

antipolysaccharide IgG responses (especially IgG2a and IgG3) induced by these glycoconjugate vaccines.

Hunter S K et al.; Biodegradable microspheres containing group B Streptococcus vaccine: immune response in mice. American journal of obstetrics and gynecology (2001 Nov), 185(5), 1174-9 describe a study to show the feasibility of producing a group B Streptococcus (GBS) vaccine, which is capable of producing both a local IgA immune response at the mucosal surface where GBS is colonized and a humoral IgG response, which is capable of transplacental passive immunization. Immunostimulatory synthetic oligodeoxynucleotides containing CpG motifs were coencapsulated as an adjuvant. PLG/GBS/CpG microparticles elicited a significantly higher GBS antibody response when compared with nonencapsulated GBS antigen or PLG-encapsulated GBS PS vaccine without the addition of the CpG adjuvant. IgG and secretory IgA (sIgA) antibodies to GBS antigen were documented in both the vaginal washings and blood samples. Thus, it was concluded that this antibody response may provide both protection against maternal GBS colonization and passive transplacental immunization for the fetus and neonate.

Lefeber, et al.; Th1-directing adjuvants increase the immunogenicity of oligosaccharide-protein conjugate vaccines related to Streptococcus pneumoniae type 3. Infection and Immunity (2003), 71(12), 6915-6920 describe Oligosaccharide (OS)-protein conjugates that are promising candidate vaccines against encapsulated bacteria, such as Haemophilus influenzae, Neisseria meningitidis, and Streptococcus pneumoniae. In the study, a minimal protective trisaccharide epitope of Streptococcus pneumoniae type 3 conjugated to the cross-reacting material of diphtheria toxin was used for immunization of BALB/c mice in the presence of different adjuvants, including CpG. The use of a combination of the adjuvants CpG and di-Me dioctadecyl ammonium bromide resulted in the highest phagocytic capacities and the highest levels of Th1-related IgG subclasses.

Von Hunolstein et al.; Synthetic oligodeoxynucleotide containing CpG motif induces an anti-polysaccharide type 1-like immune response after immunization of mice with Haemophilus influenzae type b conjugate vaccine. International Immunology (2000), 12(3), 295-303 studied the role of CpG as adjuvants in the immune response to polysaccharides (CHO) The anti-CHO IgG subclasses showed a significant increase of IgG2a and IgG3 in the presence of CpG. CpG

caused a rapid release of IL-12 and IFN in sera from treated mice. The authors concluded in the abstract that the data demonstrate that CpG have the potential to increase host antibody response against both the CHO and the protein component of a conjugated vaccine.

Mariotti Sabrina et al.; Immunogenicity of anti-Haemophilus influenzae type b CRM197 conjugate following mucosal vaccination with oligodeoxynucleotide containing immunostimulatory sequences as adjuvant. Vaccine (2002 May 22), 20(17-18), 2229-39 demonstrated that CpG ODN have the potential to increase host local and systemic antibody response against both the PRP and the protein component of a conjugated vaccine when mucosally administered in mice. Mucosal administration of Hib-CRM vaccine induced anti-PRP and neutralizing anti-diphtheria toxin antibodies of all the IgG subclasses, with a predominance of type-1 immune response-associated IgG2a and IgG3.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §102(b)

Claims 37 and 46-54 have been rejected under 35 USC 102(b) as being anticipated by Tokunaga et al. According to the Examiner Tokunaga et al describe immunostimulatory oligonucleotides and "the examples disclose method of administering the CpG to a subject and administering the CpG and an antigen to a subject (see examples). Applicants disagree with the characterization of the Tokunaga et al teachings.

Tokunaga et al describe a class of immunostimulatory palindrome containing oligonucleotides that are useful for inducing IFN-gamma and NK cell activation. Tokunaga et al do not teach or suggest the use of the immunostimulatory oligonucleotides described therein as a vaccine adjuvant. Applicants are not aware of any teachings in Tokunga et al., including the Examples, where an immunostimulatory oligonucleotide is administered in conjunction with an antigen. The claimed invention relates to a method for stimulating a subjects response to a vaccine by administering an immunostimulatory oligonucleotide adjuvant as a vaccine adjuvant to the subject to stimulate the subject's response to the vaccine. Thus, the claimed invention requires the administration of a vaccine, which is minimally composed of an antigen, and an

immunostimulatory oligonucleotide as an adjuvant. The claims are not anticipated by Tokunaga et al.

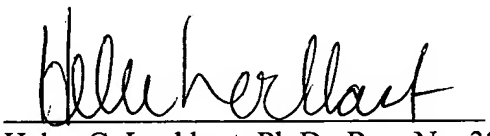
Applicants acknowledge that claims 38-45 and 55-56 have not been rejected in view of prior art.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

Applicant hereby requests a Two-Month Extension of Time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

By: 

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